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Comparison of efficacy and tolerability of single agent and double agent chemotherapy regimens in first-line treatment of elderly patients with HER-2 negative metastatic gastric cancer

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ABSTRACT

Aims: Chemotherapy remains a cornerstone in treating metastatic gastric cancer (GC), yet the management of elderly patients, who often face distinct challenges, lacks comprehensive guidelines. The aim of this study was to compare the efficacy and side effects of single-agent and double-agent chemotherapy regimens in first-line treatment of elderly patients with HER-2 negative metastatic GC.

Methods: We retrospectively evaluated HER-2 negative metastatic GC patients aged 80 years and older who were treated at Van Yüzüncü Yıl University Medical Faculty Dursun Odabaşı Medical Center Oncology Clinic between 2010 and 2023. Demographic characteristics, treatment regimens and responses, prognostic factors, grade 3-4 toxicity, progression-free survival (PFS), and overall survival (OS) were analyzed.

Results: The mean age of 56 patients was 82.6±2.3 years and 24 (42.9%) of them were women. Single-agent chemotherapy was administered to 33 (58.9%) patients, while 23 (41.1%) received double-agent chemotherapy. The median OS was 5 months (95% CI, 2.9 to 7.1) in the single-agent group and 10 months (95% CI, 4.2 to 15.8) in the double-agent group (p=0.237), although there was a numerical difference, it was not statistically significant. Median PFS was longer with double-agent chemotherapy, but not statistically significant (6 months vs. 4 months, p=0.668). No statistically significant difference was found in the side effect rates of patients receiving single and double-agent chemotherapy.

Conclusion: In our study, despite the absence of statistical significance in the survival rates among patients receiving double chemotherapeutic agents, their survival was twice as long as that of individuals receiving a single agent. Furthermore, no significant differences in terms of side effects were observed. These findings suggest that, even in individuals aged 80 years and older, a preference for double-agent chemotherapy should be considered when feasible.

Keywords: Chemotherapy, gastric cancer, elderly, first-line treatment

INTRODUCTION

Gastric cancer (GC) is a significant disease worldwide. With over one million new cases each year, it is the fifth most diagnosed malignancy globally. The mortality rate from GC is high as it is often at an advanced stage when diagnosed, and it is the third most common cause of cancer-related deaths with 768,793 deaths worldwide in 2020.[1]

Chemotherapy (CT) is the mainstay of treatment for metastatic GC and the median overall survival (OS) for patients treated with conventional chemotherapy is around 12 months.[2] The National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) guidelines recommend palliative chemotherapy for patients with HER2-negative locally advanced or metastatic GC with adequate organ function and immunotherapy as an adjunct for patients with accessibility.[3,4]

Age is one of the biggest risk factors for cancer and the incidence of most solid organ tumors increases with age. In the United Kingdom, more than one-third of new cancer diagnoses occur in individuals aged 75 and older each year, and it is expected that the number of elderly individuals living with cancer will triple from 2010 to 2040.[5] Aging is associated with a progressive decline in functional reserves and an increase in the prevalence of chronic diseases and cancer incidence. Increasing age is also associated with changes in the pharmacokinetics and pharmacodynamics of cancer treatment and increased susceptibility to treatment

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complications.[6] Therefore, appropriate patient selection is crucial to deliver cancer treatment both effectively and safely.

Current guidelines for the management of GC are predominantly based on evidence from clinical trials in younger patients, but it has been shown that elderly cancer patients have worse OS compared to younger patients.[7] In a study evaluating patients aged 75 and older with metastatic GC, it has been demonstrated that chemotherapy is effective, and its side effects are tolerable.[8] In another retrospective study, 306 patients receiving chemotherapy treatment were divided into two categories under and over 70 years of age and no statistically significant difference was found in progression-free survival (PFS) and OS between the two groups.[9]

The aim of our study was to compare the efficacy and side effects of single-agent and double-agent chemotherapy regimens in the first-line treatment of patients with HER-2 negative metastatic GC aged 80 years and older, which is part of our routine practice.

METHODS

This study was conducted in accordance with the Declaration of Helsinki. The required approval for conducting the study was obtained from the Ethics Committee of Van Training and Research Hospital, University of Health Sciences (Date: 16.08.2023, Decision No: 2023/17-03).

We retrospectively evaluated HER-2 negative metastatic GC patients aged 80 years and older who were treated at Van Yüzüncü Yıl University Medical Faculty Dursun Odabaşı Medical Center Oncology Clinic between 2010 and 2023. Patients who were 80 years of age or older, had cytologically or histologically proven recurrent or metastatic GC, received at least two cycles of chemotherapy, were HER-2 negative, and received single or double-agent chemotherapy regimens were included in the study. Patients younger than 80 years of age, without a pathological or cytologic diagnosis, previously treated for metastatic/recurrent disease, without adequate physiologic organ function, not receiving chemotherapy or receiving one cycle of chemotherapy, receiving triple combination chemotherapy regimen, HER-2 positive, receiving any treatment other than chemotherapy, and patients with unavailable data were excluded.

Demographic characteristics, treatment regimens and responses, prognostic factors, grade 3-4 toxicity, PFS, and OS were analyzed. Patients were divided into two groups: single-agent chemotherapy and double-agent chemotherapy. PFS was determined by measuring the duration from the initiation of first-line treatment to the date of disease progression, death, or the last recorded visit for non-progressing patients. OS was calculated based on the duration from the commencement of first-line treatment to the date of death or last follow-up. Radiologic evaluations were performed every 8 weeks with computed tomography scans of the thorax and abdomen or PET-CT. Treatment response was evaluated according to RECIST 1.1. Toxicity assessment was performed according to the common criteria of the National Cancer Institute. Accordingly; it was graded as follows: 1: mild, 2: moderate, 3: severe, 4: very severe.

Statistical Analysis

Categorical variables were presented as numbers (percentages), while continuous variables with normal distribution were presented as mean±standard deviation (SD); non-normal variables were reported as median (minimum-maximum). As the quantitative variables did not follow a normal distribution, the Mann-Whitney U test was employed to compare two independent groups. To compare proportions in different groups, the Chi-square test was used. Survival analyses were conducted using the Kaplan-Meier method. Prognostic factors for survival were investigated through Cox regression analysis. A p-value of less than 0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics for Windows, version 15 (IBM Corp., Armonk, N.Y., USA).

RESULTS

A total of 56 patients, 32 (57.1%) males and 24 (42.9%) females, were included. The mean age was 82.6±2.3 years. In 64.3% of the patients, liver metastases were detected, while 21.4% had lung metastases, and 25% exhibited peritoneal metastases. Demographic and disease characteristics of the patients are summarized in **Table 1**. 33 (58.9%) patients received single-agent chemotherapy and 23 (41.1%) patients received double-agent chemotherapy. 14.3% of patients responded to first-line treatment. Treatment and follow-up of the patients are summarized in **Table 2**. There were no significant differences in laboratory values between the two groups (p>0.05).

Table 1. Demographic and clinical characteristics of the patients

	All patients (n = 56)
Age, years	82.6±2.3
Gender, female	24 (42.9)
HT	27 (48.2)
DM	7 (12.5)
ECOG PS	
0	4 (7.1)
1	22 (39.3)
2	27 (48.2)
3	3 (5.4)
History of surgery	
No	51 (91.1)
Yes	5 (8.9)
Surgery type	
Curative	3 (60)
Palliative	2 (40)
Adjuvant treatment	
No	44 (86.3)
Yes	7 (13.7)
Tumor Localization	
Cardia	17 (30.9)
Corpus	12 (21.8)
Antrum	20 (36.4)
Diffuse	6 (10.9)
Metastatic organ count	
1	38 (67.9)
2	16 (28.6)
3	2 (3.6)
Metastatic organ site	
Liver	36 (64.3)
Lung	12 (21.4)
Bone	2 (3.6)
Periton	14 (25)
Brain	-
Other	9 (16.1)

Data are given as n (%), mean ± SD. HT, hypertension; DM, diabetes mellitus; ECOG PS, Eastern Cooperative Oncology Group performance status

Table 2. Treatment patterns and responses of patients

	All patients (n=56)
Chemotherapy regimen	
Single-agent	33 (58.9)
Double-agent	23 (41.1)
Chemotherapy regimen	
Capecitabine	25 (44.6)
CapeOX	3 (5.4)
FUFA	4 (7.1)
FOLFOX	12 (21.4)
Cisplatin + 5-fluorouracil	8 (14.3)
Paclitaxel	4 (7.1)
Total number of CT cycles	3 (2-12)
Dose reduction	
No	38 (67.9)
Yes	18 (32.1)
Dose delay	
No	39 (69.6)
Yes	17 (30.4)
First-line treatment response	
CR	1 (1.8)
PR	7 (12.5)
SD	11 (19.6)
PD	37 (66.1)
Progression	
No	6 (10.7)
Yes	50 (89.3)
Second-line treatment	8 (14.3)
Follow-up period, months	5.5 (2-58)
Final situation	
Alive	13 (23.2)
Dead	43 (76.8)

Data are given as n (%), median (minimum-maximum). CapeOX, capecitabine and oxaliplatin; FUFA, 5-fluorouracil and folinic acid; FOLFOX, folinic acid, 5-fluorouracil, and oxaliplatin; CT, chemotherapy; CR, complete response; PR, partial response; SD, stabil disease; PD, progressive disease

Capecitabine, 5-fluorouracil, and folinic acid (FUFA), or paclitaxel were used as single-agent chemotherapy. Folinic acid, 5-fluorouracil, and oxaliplatin (FOLFOX) or capecitabine and oxaliplatin (CapeOX) were used as a double chemotherapy regimen. The median overall survival was 5 months (95% CI, 2.9 to 7.1) in the single-agent group and 10 months (95% CI, 4.2 to 15.8) in the double-agent group (p=0.237), although there was a numerical difference, it was not statistically significant (**Figure 1**). The survival percentages for single-agent chemotherapy at 6 months, 12 months, and 36 months were 43%, 31.8%, and 9.3%, respectively; whereas for double-agent chemotherapy, the survival percentages at 6 months, 12 months, and 36 months were 65.2%, 42.5%, and 31.0%, respectively. Median PFS was longer with double-agent chemotherapy, but not statistically significant (6 months vs. 4 months, p=0.668) (**Figure 2**). No statistically significant difference was found in the side effect rates of patients receiving single and double-agent chemotherapy (**Table 3**).

Table 3. Treatment-Related Adverse Events

Adverse event	Single-agent CT	Double-agent CT	p
Grade 3-4 neutropenia	0	3 (13)	0.064
Grade 3-4 anemia	9 (27.3)	3 (13)	0.322
Grade 3-4 thrombocytopenia	0	1 (4.3)	0.411
Grade 3-4 mucositis	2 (6.1)	0	0.507
Grade 3-4 diarrhea	4 (12.1)	0	0.136
Grade 3-4 nausea-vomiting	4 (12.1)	1 (4.3)	0.639
Grade 3-4 peripheral sensory neuropathy	0	1 (4.3)	0.411
Grade 3-4 allergic reaction	1 (3)	1 (4.3)	1
Grade 3-4 thrombosis	1 (3)	1 (4.3)	1
Grade 3-4 hepatotoxicity	0	0	-
Grade 3-4 nephrotoxicity	3 (9.1)	0	0.261
Grade 3-4 cardiotoxicity	0	0	-

Data are given as n (%). CT, chemotherapy

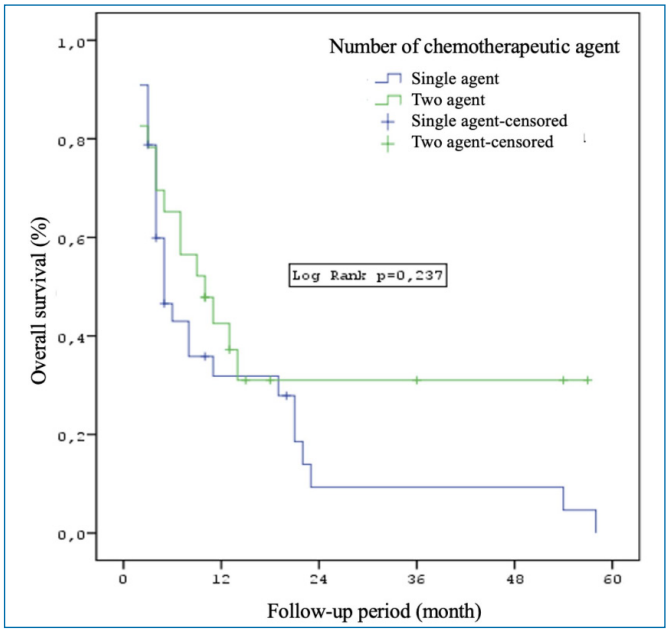

Figure 1. Survival curve for overall survival comparison between chemotherapy regimens

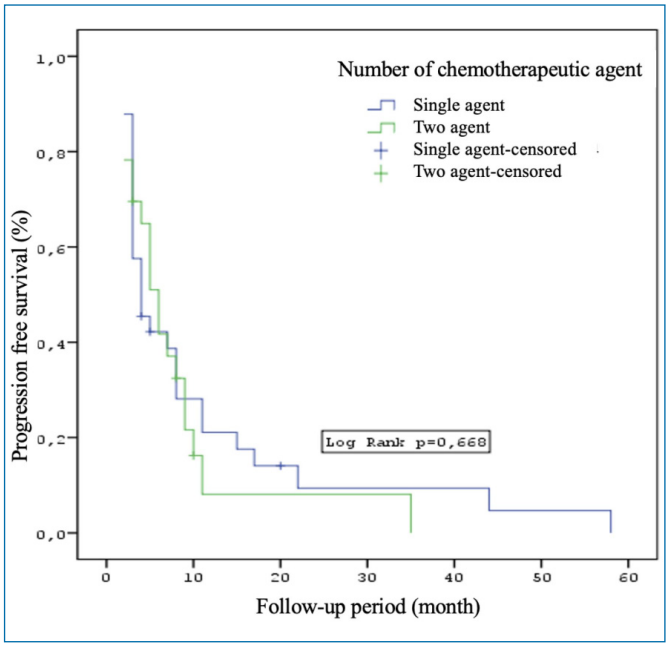

Figure 2. Survival curve for progression-free survival comparison between chemotherapy regimens

DISCUSSION

In our study, we found no statistically significant difference between double chemotherapy regimens and single chemotherapy regimens in terms of survival and side effects in the first-line treatment of patients aged 80 years and older with HER-2 negative metastatic/recurrent GC.

The survival benefit of systemic therapy, in addition to the best supportive care, compared with the best supportive care alone in patients with advanced GC has been demonstrated in several randomized trials.[10-12] In a comparison between chemotherapy and best supportive care, patients who received chemotherapy in addition to best supportive care for advanced GC had longer OS (8 vs. 5 months) and PFS (5 vs. 2 months).[10] In a meta-analysis by Wagner et al.[13] those receiving combination therapy for metastatic disease had an overall survival benefit compared to those receiving monotherapy. Also, as expected, the

frequency of side effects was higher in patients receiving combination therapy compared to monotherapy. In a phase III randomized trial, the addition of docetaxel to cisplatin-fluorouracil therapy improved radiological response rates and OS but was associated with significantly increased toxicity.[14]

The ESMO gastric cancer guideline supports dose-reduced oxaliplatin-based chemotherapy for elderly or frail patients, based on results from the phase III GO-2 trial15 showing lower toxicity and comparable survival outcomes compared to standard dose.[4] In a phase 2 study by Graziano et al.[16] evaluating cisplatin plus 5-fluorouracil treatment in GC patients aged 65 years and older, 58 patients were studied and the disease control rate was 43%, and grade 3-4 neutropenia was seen in 17% of patients. In our study, grade 3-4 neutropenia and grade 3-4 anemia were detected in 13% and 13% of patients using double-agent chemotherapy, respectively.

In a retrospective analysis using data from 3 large randomized trials, 257 of 1080 patients with gastro-oesophageal cancer were over 70 years of age. Response rates, overall survival, and incidence of grade 3 or 4 toxicity were similar between the two age groups, suggesting that patients over 70 years of age derive a similar benefit from chemotherapy to younger patients. Patients over 70 years of age received lower doses of chemotherapy, so results showing no increase in toxicity with age should be interpreted with caution.[17] In a phase III study in Korea in patients aged 70 years and older, adding oxaliplatin to capecitabine showed a survival benefit with acceptable toxicity.[18] In a study evaluating 178 patients aged 70 and older with metastatic GC, the use of single-agent and combination therapy was compared in the first-line treatment. No statistically significant difference was observed in PFS and OS.[19] In our study, although the survival between the groups was not statistically significant, the survival of patients using double agents was 5 months longer than those using single agents. This is extremely important for this disease and age group.

Despite the limitations of our study, including being single-center and retrospective, as well as having a relatively small sample size, it is noteworthy as the first study conducted in this patient group based on our review of the literature. Furthermore, our patient group was highly homogeneous, as HER-2 positive patients and those receiving treatment other than chemotherapy were excluded from the study. In the future, larger-scale, prospective, and well-designed studies are needed in this patient group.

Limitations

It was a retrospective study conducted in a single institution with a relatively small number of patients.

CONCLUSION

In our study, although the survival of patients receiving double chemotherapeutic agents did not reach statistical significance, the survival was twice that of patients receiving a single agent, and there was no statistically significant difference in terms of side effects. This indicates that even at the age of 80 years and over, we should be inclined to give a double agent if possible.

ETHICAL DECLARATIONS

Ethics Committee Approval

The required approval for conducting the study was obtained from the Ethics Committee of Van Training and Research Hospital, University of Health Sciences (Date: 16.08.2023, Decision no: 2023/17-03).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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